REMARKS

Claims 1-62 were pending in the present application. Claims 1-21, 31-59, and 62 were withdrawn from consideration. By virtue of this response, claims 22, 25 and 28 have been amended. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. No new matter has been added.

Support for the amendment of claims 22 and 25 can be found throughout the specification and claims as originally filed and, in particular, on pages 2-3 (bridging paragraph); page 3, lines 6-15 & 20-27; pages 3-4 (bridging paragraph); pages 6-7 (bridging paragraph); page 7, lines 16-27; page 8 in its entirety; page 15, line 12 through page 17, line 31 (especially lines 10-20 of page 16 and lines 12-14 of page 17); pages 26-30; and claims 12, 15, 23, 33, 41, and 45, as originally filed.

The structure at the bottom of page 14 and claim 28 has been amended to correct a typographical error. Both the error, and its correction, would have been obvious to one of skill in the art, as the structure of polysorbates is well known to those of skill and clearly identified in the text as the structure shown in paragraph 55 and claim 28. For the Examiner's convenience, the Applicants provide the Merck Index entry (7742) for polysorbate 80. *The Merck Index, 12th Edition*, 1996, Published by Merck Research Laboratories, which would have been available to one of skill at the time of filing of the present application.

In view of the amendment of claim 28 to correct the typographical error brought to the Applicant's attention by the Examiner's withdrawal of claim 28, the Applicants respectfully request that claim 28 not be withdrawn, as the elected species, polysorbate 80 falls within the scope of claim 28 when w+x+y+z is 20.

Regarding the Information Disclosure Statements

The Applicants thank the Examiner for his review of the cited references and return of the signed PTO-1449 forms.

Objection to the specification

The specification has been amended to correct the typographical error noted by the Examiner.

Rejections under 35 U.S.C. §112 second paragraph

Claim 25 is rejected under 35 U.S.C. §, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

While not agreeing with the Examiner's rejection, the Applicants have amended claim 25 in accordance with the Examiner's suggestion in order to further prosecution of the present application. The Applicants respectfully request the withdrawal of the rejection of claim 25.

Rejections under 35 U.S.C. §103

A. Claims 22-27, 29, 30, 60, and 61 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Andya (USP 6,267,958).

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

The Examiner alleges that one of skill would be motivated to combine the echinocandins of the primary references (Debono, Burkhardt, Chen, Balkovec or Abbot) with Andya to achieve the

claimed formulations. Andya describes and claims formulations for the stabilization of proteins and is not relevant to the formulation of echinocandins. In fact, Andya teaches away from the use of the formulations disclosed to stabilize bioactive agents such as echinocandins, which are excluded from the description of the "proteins," as is clearly stated in col. 6, lines 38-43, where Andya defines proteins as:

> a sequence of amino acids for which the chain length is sufficient to produce the higher levels of tertiary and/or quaternary structure. This is to distinguish from "peptides" or other small molecular weight drugs that do not have such structure. Typically the protein herein will have a molecular weight of at least about 15-20 kD, preferably at least about 20 kD.

Echinocandins are not "proteins" as described in Andya, cannot achieve the tertiary or quaternary structure described in the above paragraph and do not meet the mass guidelines set forth in Andya. Thus, the Applicants fail to see how one of skill would be motivated to combine the primary references with Andya to achieve the claimed formulations and respectfully request the withdrawal of the rejection of claims 22-27, 29, 30, 60, and 61.

B Claims 22-27, 29, 30, 60, and 61 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Horikoshi (USP 4348384).

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

As with the previous rejection, the Examiner alleges that one of skill would be motivated to combine the echinocandins of the primary references (Debono, Burkhardt, Chen, Balkovec or Abbot) with Horikoshi to achieve the claimed formulations. The formulations of Horikoshi differ from the claimed formulations in several important respects, including that the Horikoshi

formulations are for the oral delivery of proteins. As noted above, one of skill in the art would not consider the echinocandins taught and described in the present claims to be a "protein" and, as is clear from the specification (see page 1, lines 15-21), the claimed echinocandin formulations are intended for subcutaneous or intravenous administration and therefore must be suitable for this purpose. One of skill in the art would have no motivation to combine the oral protein formulations of Horikoshi with the echinocandins of the primary references, and there is no suggestion or teaching in the references to do so. As it is well known in the art that the requirements for oral and intravenous or subcutaneous formations vary greatly, one of skill would not seek to combine the echinocandins of the present invention with an oral formulation with an expectation of achieving a successful intravenous or subcutaneous formulation with increased stability. This is particularly the case for echinocandins, which are known to be of low stability and low water solubility (see page 2, lines 1-15) and thus particularly difficult to formulate for oral delivery. It is unlikely that one of skill would seek to combine conventional oral formulations with echinocandins, given the low probability of success in view of what is known of echinocandins and the difficulties associated with their formulation.

Additionally, there is nothing to suggest in the references that the combination suggested by the Examiner would lead to the surprising effects and enhanced stability observed in the presently claimed formulations and described in the present application. The unexpectedly enhanced stability afforded by the presently claimed formulations are shown in Tables 3 and 4 of the present application. It is not appropriate to use hindsight and knowledge of the Applicant's specification to predict a combination of references which would lead to a successful formulation.

Further, as known to those of skill in the art, and as commented on at length by Boulhoumie (see below), the preparation of advantageous, stabilizing formulations, particularly those appropriate to use with lyophilization, for bioactive agents in general is very unpredictable. This is even more so the case with the echinocandin class of compounds which are known to be chemically unstable and of limited solubility.

In view of the above arguments, the Applicants request the withdrawal of the rejection of claims 22-27, 29, 30, 60, and 61.

C. Claims 22-27, 29, 30, and 60 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Staniforth (USP 6,153,224)

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

The formulations described in Staniforth are clearly described as being for use in the administration of respiratory drugs via inhalation into the lungs. As is well known to those of skill in the art, the requirements for formulations to be administered via inhalation are greatly different from those to be administered intravenously or via subcutaneous injection, as it taught in the present application. Further, as noted throughout the present specification, particularly the Examples and Tables 3 and 4, the presently-claimed formulations result in surprisingly enhanced stability and prolonged shelf life for the claimed echinocandin formulations. As noted by the Examiner, there is no suggestion to use the respiratory formulations of Staniforth with echinocandins to produce *e.g.*, an anti-fungal formulation that is stable and suitable for injection or intravenous delivery. It is well known to those in the art and described in the specification (see page 2, lines 1-15), that echinocandins are low in stability and water solubility and one of skill would not be motivated to overcome these difficulties or have a likelihood of success by using inhalation formulations with the echinocandins.

Additionally, there is no suggestion in Staniforth that the formulations would be suitable for freeze drying and form a suitable "cake" which can be used in pharmaceutical administration. As can be clearly seen in Table 1, final column, of the present application, not all formulations result in suitable "cakes."

Further, as known to those of skill in the art, and as commented on at length by Boulhoumie (see below), the preparation of advantageous, stabilizing formulations, particularly those appropriate to use with lyophilization, for bioactive agents in general is very unpredictable. This is even more so the case with the echinocandin class of compounds which are known to be chemically unstable and of limited solubility.

In view of the above arguments, the Applicants respectfully request withdrawal of the rejection of claims 22-27, 29, 30, 60, and 61.

D. Claims 22-27, 29, 30, 60, and 61 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Tarara (USP 6565885).

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

Tarara teaches methods and formulations suitable for "spray drying" which is not the same as lyophilization. Not only are the requirements for these types of formulations different, but the spray dry formulations and methods taught in Tarara are unsuitable for use with echinocandins. As noted in clams 20-23 of Tarara, temperatures of > 40 °C are used in the spray dry process. It is clearly taught in the present application (see page 2, lines 1-15) that echinocandins are known to be unstable and would generally degrade quickly at such temperatures. Thus, one of skill, contrary to the Examiner's assertions, would be unlikely to combine the teachings of Tarara with the echinocandins of the primary references. As noted above for Staniforth, Tarara also teaches formulations that are suitable for inhalation and pulmonary delivery. There is no implicit or explicit suggestion for the echinocandins to be suitable for use in such formulations, nor would one of skill, absent hindsight based on the present specification, have any expectation of success in achieving higher stability formulations of echinocandins using the disclosed formulations of Tara.

Further, as known to those of skill in the art, and as commented on at length by Boulhoumie (see below), the preparation of advantageous, stabilizing formulations, particularly those appropriate to use with lyophilization, for bioactive agents in general is very unpredictable. This is even more so the case with the echinocandin class of compounds which are known to be chemically unstable and of limited solubility.

In view of the above arguments, the Applicants respectfully request withdrawal of the rejection of claims 22-27, 29, 30, 60, and 61.

E. Claims 22-27, 29, 30, 60, and 61 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Backstrom (USP 5,952,008).

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

As with Tarara and Staniforth, the teachings of Backstrom are specifically directed to formulations suitable for the administration of bioactive materials via the respiratory system, particularly through the lungs. In fact, in the Background of the Invention, Backstrom distinguishes the formulations described from those used for intravenous or subcutaneous delivery. Thus, rather than a teaching to combine Backstrom with the echinocandins of the primary references, Backstrom itself is teaching away from such a combination, that is, the Backstrom formulations and teachings of the reference would not lead one of skill in the art to expect a successful stabilizing formulation to be achieved.

In addition, it is noted that Backstrom generically discloses "surfactants" but provides no motivation to one of skill to select "micelle-forming" surfactants as presently claimed by the Applicants. It is noted throughout the present specification that is the particular combination of the formulation with the echinocandins which leads to the unexpected stability of the claimed formulations and their suitability for lyophilization.

Further, as known to those of skill in the art, and as commented on at length by Boulhoumie (see below), the preparation of advantageous, stabilizing formulations, particularly those appropriate to use with lyophilization, for bioactive agents in general is very unpredictable. This is even more so the case with the echinocandin class of compounds which are known to be chemically unstable and of limited solubility.

In view of the above arguments, the Applicants respectfully request withdrawal of the rejection of claims 22-27, 29, 30, 60, and 61.

F. Claims 22-27, 29, 30, 60, and 61 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Bernstein (USP 6,689,390).

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

As noted by the Examiner, there is no suggestion to use echinocandins in the methods and formulations described in Bernstein. Additionally, the formulations of Bernstein are directed to altering the release kinetics of the bioactive agents by incorporation within a "microparticle" formed by a polymer matrix (see Abstract; col. 2, lines 17-25, etc.), whereas the claimed formulations of the present invention are not microparticles, but instead are microemulsions. The reference particularly distinguishes itself from formulations where the non-bioactive agents are used as "excipients" (see col. 2, lines 9-11) and thus from the present formulation where the echinocandin, bulking agent and surfactant are co-mixed. Thus, the reference appears to teach away from any combination which would result in the presently claimed formulations.

Additionally, while numerous agents are listed for inclusion with the "microparticles", there is no suggestion of combining the particular constituents of the claimed formulations and no suggestion that a "micelle-forming" surfactant, as claimed, should be selected from among the many listed choices.

Further, as known to those of skill in the art, and as commented on at length by Boulhoumie (see below), the preparation of advantageous, stabilizing formulations, particularly those appropriate to use with lyophilization, for bioactive agents in general is very unpredictable. This is even more so the case with the echinocandin class of compounds which are known to be chemically unstable and of limited solubility.

In view of the above arguments, the Applicants respectfully request withdrawal of the rejection of claims 22-27, 29, 30, 60, and 61.

G. Claims 22-27, 29, 30, 60, and 61 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Bouloumie (USP 6,284,277).

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

Bouloumie describes at length (col. 4, lines 5-28, reproduced below) the unpredictability of various excipients and additives when used alone, or in combination, during the process of freeze drying and with various bioactive agents, and further states that the synergistic effect described in this reference results from a particular combination of additives with bioactive agents.

> In conclusion, the scientific literature on the subject of the effect of ***excipients on the stabilization of pharmaceutical active ingredients gives contradictory information on their properties and furthermore does not make it possible to obtain some information on the subject of the relationships between the structure of a freeze-dried product and its stability***. Likewise, the role of the polyols and of the amino acids, alone or in combination, ***is not described according to a set of generalizable properties, but has been observed with contradictory results according to the active principles studied and the quantities of excipients used***.
>
> It has now been found that a synergistic effect exists between mannitol and alanine on the stabilization of freeze-dried pharmaceutical active ingredients. It has in particular been demonstrated that this synergistic effect exists only in

a narrow range of relative concentrations of each of these two excipients.

> The discovery of a surprising synergistic effect resulting from the coexistence of an amorphous phase and a crystalline phase which has the consequence of stabilizing the freeze-dried pharmaceutical active ingredient forms the basis of the present invention. The present invention therefore describes the production of this effect for specific mannitol/alanine ratios. (Col. 2, lines 5-28; Emphasis Added)

As stated in the reference, the synergistic effect described is dependent on the ratio of mannitol and alanine. The Applicant's present application and pending claims do *not* require alanine to achieve the unexpected effects described and taught (see *e.g.,* Tables 3 and 4). From the teaches of the reference, one of skill would expect that alanine was a *necessary* ingredient for the successful lyophilized formulation and would not have been motivated to formulate the claimed compositions.

In view of the above arguments, the Applicants respectfully request withdrawal of the rejection of claims 22-27, 29, 30, 60, and 61.

H. Claims 22-27, 29, 30, 60, and 61 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Weers (USP 6,309,623).

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

Once again, the Examiner suggests that one of skill in the art would be likely to formulate echinocandins, which are known to be difficult to formulate due to instability and insolubility, using the teachings of a reference directed to formulations for inhalation. As noted in Boulhoumie, above, and in the present application and as is known to those of skill, it is not predictable whether a particular combination of active and inactive ingredients will result in stable lyophilized formulations. There is no suggestion in the Weers reference, as noted by the Examiner, that the formulations would be suitable for use with echinocandins, nor that lyophilization would

result in a well-formed cake and stable formulation. Additionally, due to the unpredictability noted in Boulhoumie, a skilled artisan, at the time of the present invention, would not have an expectation for success, let alone be able to predict the increased stability and prolonged shell life unexpectedly afforded by the claimed formulations.

There is no suggestion in the reference to select the micelle-forming surfactants as claimed in the present application and, indeed, the reference teaches that certain surfactants claimed in the present application are *unsuitable* for use in the Weers formulations (see below), thus, the reference teaches away from the formulations of the present application.:

> In contrast to prior art attempts to provide stabilized suspensions which require excipients (i.e. surfactants) that are soluble in the suspension medium, the present invention provides for stabilized dispersions, at least in part, by immobilizing the bioactive agent(s) and excipients within the structural matrix of the hollow, porous microstructures. Accordingly, preferred excipients useful in the present invention are substantially insoluble in the suspension medium. Under such conditions, ***even surfactants like, for example, lecithin cannot be considered to have surfactant properties in the present invention*** since surfactant performance requires the amphiphile to be reasonably soluble in the suspension medium. (Col. 10, lines 49-61; Emphasis added.)

In view of the above arguments, the Applicants respectfully request withdrawal of the rejection of claims 22-27, 29, 30, 60, and 61.

I. Claims 22-27, 29, 30, and 60 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Staniforth (USP 6,475,523).

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

As noted previously, one of skill in the art would not be motivated to combine the teachings of Staniforth, which are directed to formulations for use in dry powder inhalers, to formulate an echinocandin formulation suitable for lyophilization and for delivery intravenously or via subcutaneous injection. The unpredictability of formulations which are suitable for lyophilization and which will result in stable bioactive ingredients and suitable "cakes" is noted above in reference to Boulhoumie. Thus, in addition to lacking any motivation to combine the references, Staniforth also does not teach the selection of "micelle-forming" surfactants and the combination with the claimed bulking agents to achieve the unexpected stability and prolonged shelf life of the echinocandin formulations described and taught in the present application.

In view of the above arguments, the Applicants respectfully request withdrawal of the rejection of claims 22-27, 29, 30, and 60.

J. Claims 22-27, 29, 30, 60, and 61 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Dellamary (USP 6433040).

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

One of skill in the art would not be motivated to combine the teachings of Dellamary, to formulate an echinocandin formulation suitable for lyophilization and for delivery intravenously or via subcutaneous injection. The unpredictability of formulations which are suitable for lyophilization and which will result in stable bioactive ingredients and suitable "cakes" is noted above in reference to Boulhoumie. Thus, in addition to lacking any motivation to combine the references, Staniforth also does not teach the particular selection of "micelle-forming" surfactants and the combination with the claimed bulking agents to achieve the unexpected stability and prolonged shelf life of the echinocandin formulations described and taught in the present application. Indeed, some of the surfactants taught in Dellamary (*e.g.*, certain block copolymers,

see claim 3) as being suitable for use in the Dellamary formulations are taught not to be suitable for the presently claimed formulations (see page 7, lines 5-11).

The Examiner has also not provided any rationale as to why one of skill would have an expectation of success in overcoming the difficulties of formulating echinocandins in general or echinocandin lyophilates in particular using the teachings of the reference.

In view of the above arguments, the Applicants respectfully request withdrawal of the rejection of claims 22-27, 29, 30, 60, and 61.

K. Claims 22-27, 29, 30, 60 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Edwards (USP 5,985,309).

In response, the Applicants respectfully traverse this rejection and submit that the Examiner has not put forth a case for *prima facie* obviousness.

As noted previously, one of skill in the art would not be motivated to combine the teachings of Edwards, which are directed to formulations for inhalers, to formulate an echinocandin formulation suitable for lyophilization and for delivery intravenously or via subcutaneous injection. The unpredictability of formulations which are suitable for lyophilization and which will result in stable bioactive ingredients and suitable "cakes" is noted above in reference to Boulhoumie. Thus, in addition to lacking any motivation to combine the references, Edwards also does not teach the selection of "micelle-forming" surfactants and the combination with the claimed bulking agents to achieve the unexpected stability and prolonged shelf life of the echinocandin formulations described and taught in the present application.

In view of the above arguments, the Applicants respectfully request withdrawal of the rejection of claims 22-27, 29, 30, and 60.

CONCLUSIONS

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **342312003601**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 11, 2004

Respectfully submitted,

By _____

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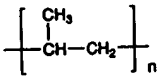
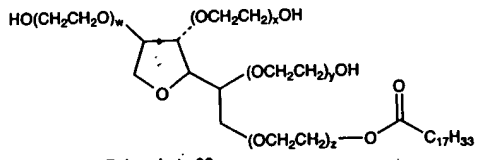


Isotactic form, *Amco, Amerfil, Beamette, Courlene PY, DLP, Gerfil, Herculon, Lambeth, Meraklon, Moplen, Olane, Prolene, Tuff-Lite, Ulstron.* Solid material, softens at ~155°, mp ~165°. Low flammability comparable to that of wool. Keeps strength down to −100°. d 0.90-0,92. Practically insol in cold org solvents. Sol in hot decalin, hot tetralin, boiling tetrachloroethane. Shrinks in boiling trichloroethylene. Resistant to acids, alkalies; attacked by strong oxidizing agents, *e.g.*, hydrogen peroxide. Good resistance to abrasion ("pilling"). Tendency to develop static charges. Unstabilized material has poor resistance to sunlight. Difficult to dye, lacks dye-attracting polar groups in structure.

USE: Isotactic form: for fishing gear, ropes, filter cloths, laundry bags, protective clothing, blankets, fabrics, carpets, yarns, etc.

7742. Polysorbates. Polyoxyethylene sorbitan esters; POE sorbitan esters. Nonionic surfactants derived from sorbitan esters, *q.v.* Comprehensive description: P. Becher, "Polyol Surfactants" in *Nonionic Surfactants,* M. J. Schick, Ed. (Dekker, New York, 1967) pp 247-299. Description of prepn and uses: L. R. Chislett, J. Walford, *Int Flavours Food Addit.* 7, 61 (1976). Pharmacology of polysorbate 80: R. K. Varma *et al., Arzneimittel-Forsch.* 35, 804 (1985). Determn in foods: H. Kato *et al., J. Assoc. Off. Anal. Chem.* 72, 27 (1989).



Polysorbate 80
(Sum of w, x, y, and z is 20)

Polysorbate 80, polyoxyethylene (20) sorbitan monooleate, POE (20) sorbitan monooleate, Emsorb 6900, Liposorb O-20, Monitan, Sorlate, T-Maz 80, Tween 80. Lemon- to amber-colored, oily liquid. d 1.06-1.09. Viscosity (25°): 300-500 centistokes. Very sol in water; sol in alcohol, cottonseed oil, corn oil, ethyl acetate, methanol, toluene. Insol in mineral oil. pH of 5% aq soln between 6 and 8. LD_{50} in mice, rats (ml/kg): 7.5, 6.3 i.p. (Varma).

USE: As emulsifiers and dispersing agents in medicinal products; as defoamers and emulsifiers in foods. Pharmaceutic aid (surfactant).

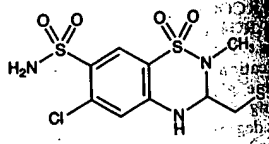
7743. Polytetrafluoroethylene. *Tetrafluoroethene homopolymer; tetrafluoroethylene polymer;* polytetrafluoroethylene resin; polytef; PTFE; Fluon; Teflon; Tetran. A highly stable thermoplastic tetrafluoroethylene homopolymer. Composed of at least 20,000 C_2F_4 monomer units linked into very long unbranched chains. Prepd by polymerization of tetrafluoroethylene: Plunkett, U.S. pat. 2,230,654 (1941 to Kinetic Chem.); Brubaker, U.S. pat. 2,393,967; Joyce, U.S. pat. 2,394,243 (both 1946 to du Pont); Hanford, Joyce, *J. Am. Chem. Soc.* 68, 2082 (1946); Renfrew, Lewis, *Ind. Eng. Chem.* 38, 870 (1946); Renfrew, U.S. pat. 2,534,058 (1950 to du Pont); C. E. Schildknecht, *Vinyl and Related Polymers* (Wiley, New York, 1952) pp 483-494. Account of discovery by Roy J. Plunkett: A. B. Garrett, *J. Chem. Ed.* 39, 288 (1962). *Reviews:* R. W. Moncrieff, *Man-Made Fibres* (John Wiley, New York, 4th ed., 1963) pp 512-517; McCane in *Encyclopedia of Polymer Science and Technology* vol. 13, N. M. Bikales, Ed. (Interscience, New York, 1970) pp 623-654; S. V. Gangal in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 11 (Wiley-Interscience, New York, 3rd ed., 1980) pp 1-24.

Nonflammable, high polyme
opaque solid (depending on the
cally. Useful temp range from
an extremely viscous gel at
monomer at temperatures above
ness 55-56. Tensile strength
lus ~80,000-90,000 psi at room
−80°. Dielectric constant (
2.05. Not affected by water, aci
acetyl chloride, boron fluoride,
of sodium hydroxide, and organ
water. No substance has been
polymer at moderate temperatu
with fluorine, hot plasticizers
recommended. Is subject to cold
cause of its high melt viscosity
niques similar to those used in
mally used for fabrication.

Caution: The finished compou
conditions. There have been repo
the symptoms of which resemble
fluenza, in humans exposed to
conditions of inadequate ventilat
smoking tobacco with polytetrafl
amounts, is to be avoided.

USE: As tubing and sheets for
process work; for lining reaction
pump packings, sometimes mixed
bers; as electrical insulator esp. in
tions; filtration fabrics; protective

7744. Polythiazide. *6-Chloro-[[(2,2,2-trifluoroethyl)thio]methyl]-2H-thiazine-7-sulfonamide 1,1-dioxide;* 2-H
ethylthiomethyl)-6-chloro-7-sulfam
benzothiadiazine 1,1-dioxide; 6-chlo
yl-7-sulphamoyl-3-(2,2,2-trifluoro
benzo-1,2,4-thiadiazine 1,1-dioxid
Renese. $C_{11}H_{13}ClF_3N_3O_4S_3$; mol wt
2.98%, Cl 8.06%, F 12.96%, N 9.55%
Prepn: J. M. McManus, U.S. pat.
er). Comprehensive description: T.
in *Analytical Profiles of Drug Substa*
Ed. (Academic Press, New York, 19

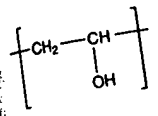


Crystals from isopropanol, mp 202-5
and acetone. Practically insol in water
in aq solns made alkaline with carbonates
the alkali metals. Rate of decompn increa
in pH.

THERAP CAT: Diuretic, antihypertensive.

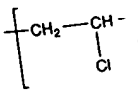
7745. Polyvinyl Alcohol. *Ethenol homopolymer;* Akwa Tears; Elvanol; Gelvatol; Liquifilm; Mowiol; viol; Sno Tears; Vinarol; Vinol. A polymer prepd polyvinyl acetates by replacement of the acetate groups hydroxyl groups. The alcoholysis proceeds most rapidly a methanol + methyl acetate mixture in the presence catalytic amounts of alkali or mineral acids: Herrm Haehnel, *Ber.* 60, 1658 (1927). *Monograph:* C. A. Schnecht, *Vinyl and Related Polymers* (Wiley, New York, 1952). The head-to-tail or 1,3-glycol structure is favored Staudinger *et al., Ber.* 60, 1782 (1927); *J. Prakt. Chem.*

Denoon, *J. Am. Chem. Soc.* 6
Kenyon, *ibid.* 62, 415 (1940);
10 (1943). *Reviews:* M. Leeds
a of Chemical Technology* vol.
w York, 2nd ed., 1970) pp
A. C. Finch, Ed. (Wiley, Ne
S. Dunn, *Chem. & Ind. (Londo*
ohol monomer has not been
mour, G. B. Kauffman, *J. Ch*



ed polyvinyl alcohol powders
ften at about 200° with deco
alcohols have different cont
s and therefore different visc
t code number following th
ree of hydrolysis, while the
the approx viscosity in cen
olyvinyl alcohols are essenti
but those coded 20-105 r
Aq solns are colloidal and
Pure aq solns are neutral or
growth. Insol in petroleun
lastics industry in molding
esistant to gasoline, textile
s; can be compounded to yi
uf artificial sponges, fuel h
plastics and glass, in phar
water-sol film and sheetin
ncreasing agent); ophthalm

yvinyl Chloride. *Chloroet*
polymer;* PVC; Geon; Bre
eal; Marvinol. Polyvinyl
er the names: *Rhovyl, I*
yl, Crinovyl, Envilon, Nip
150,000. Prepn: Baum
enfeld, U.S. pat. 2,168,
tructure: Natta, Rigamo
e, *mat. nat.* 24, 381 (1
el *et al., J. Am. Chem.*
E. Schildknecht, *Vinyl*
York, 1952) pp 392-442
Technology* (Maclaren,
L. Gardner, "Vinyl Pol
cyclopedia of Chemica
cience, New York, 3rd
vetnick, *Polyvinyl Chl*
New York, 1969).



olid. d 1.406; *n* 1.54.
iscoloration from expo
nmodified polyvinyl c
ne, methyl cyclohexa
ene, tetrahydrofuran,
for lower polymers: d
methyl isobutyl keto
ne, dioxane, methyle
Rubber substitutes, e
able thin sheeting, fil
le upholstery, rainco
ts.

Pomegranate. G
N *Punica granatum* L
region; Eastern, Wes
subtropical countr
ng of pelletierine, m